## REMARKS

Claims 35-54 are pending and stand rejected. No claim amendments are presented. Applicants request entry of the following Remarks and reconsideration and withdrawal of the outstanding rejections and objections. In the event that all of the claim rejections and objections are not withdrawn, Applicants request entry of the present Response After Final to place the application in better condition for appeal.

### Claim Rejections

*Claim Rejections under 35 USC §102*

Claims 35-40, 42, 45, 49-50 and 52-53 stand rejected under 35 USC §102(e) for allegedly being anticipated by U.S. patent 6,369,039 ("Palasis"). The Office Action asserts that Palasis discloses a method of delivering a bioactive material from an implantable medical device having a balloon with a bioactive material "on an outer surface of the balloon" (Office Action at page 3) and that this bioactive material is "the coating per se, i.e. no other material and by fluid delivery to the surface of the balloon..." and that "the [bioactive] agent is the coating per se or the fluid drug" (Office Action at page 3).

Applicant respectfully traverses this rejection. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (MPEP 2131). Palasis does not teach or suggest that a bioactive material *on an outer surface* of a balloon is maintained *on the outer surface of the inflated balloon in contact with the inner wall of a body vessel while the balloon is inflated* (claim 35), or *inflating the*

*balloon to deliver* the bioactive material from a *coating consisting of the bioactive material,* in order to *deliver the* bioactive material *while maintaining the* bioactive agent *in direct contact with the inner wall of the body vessel* (claim 49) in a coating that is also *free of a containment layer* or *containment material* (claims 35 and 49).

The Office Action (page 3) mischaracterizes the Palasis reference by selectively citing the underlined portion of a sentence found at col. 3, lines 12-20, which reads:

> The substantially saturated solution is "associated with" the medical device in that the therapeutic agent is held in a cavity(ies) of the device, such as in an infusion style catheter such as a channel balloon; or the therapeutic agent is coated onto the surface of the device as a coating per se or as part of a coating; or the substantially saturated solution is held within or passes through the medical device, such as in a needle injection catheter (Palasis, col. 3, lines 12-20, emphasis added).

Palasis, when read in its entirety, requires administering the "saturated solution" of the bioactive from a catheter as a liquid or incorporating the bioactive into a containment material within a coating. The therapeutic agent of Palasis cannot be maintained within a coating at the desired concentration as a "substantially saturated" solution in the absence of a containment material. Specifically, Palasis teaches the delivery of a therapeutic agent in "a substantially saturated solution" and "releasing a volume of the solution of therapeutic agent from the medical device" (Palasis, col. 1, lines 50-55). Palasis discloses drug delivery catheters where the "delivery of therapeutic agents is thus achieved by controlling the concentration of therapeutic agent at a target location, rather than

relying on a pressure-driven process" (Palasis, col. 2, lines 51-54). Throughout the Palasis reference, Palasis teaches that delivery of a "substantially saturated" solution of the bioactive is critical to deliver the therapeutic agent, explaining that "[b]ecause the solution is substantially saturated, the concentration gradient of therapeutic agent resulting from injection drives the therapeutic agent deep into tissue by diffusion... the method of the present invention achieves deep tissue penetration by a concentration driven mechanism" (col. 7, lines 35-43). Indeed, Palasis indicated that "the inventors have determined that concentration of therapeutic agent is the critical parameter for transport, and thus... therapeutic effect, in a vessel wall" (Palasis, col. 13, lines 34-36, emphasis added). Nowhere does Palasis teach or suggest the incorporation of the therapeutic agent in a balloon coating that is free of a containment layer or material. In each of the examples, Palasis describes administration of a therapeutic agent as a solution of the therapeutic agent either ejected from an infusion catheter, or applied to a "hydrogel coating" (col. 10, lines 20-34) that forms a containment material layer.

Since "a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention" (MPEP 2141.02), Applicants respectfully submit that Palasis does not anticipate the embodiments of the present invention claimed in claims 35 and 49. All of the remaining claims rejected under 35 USC §102(e) depend from either claim 35 or 49. For at least the reasons above, Applicants request reconsideration and withdrawal of this rejection.

*Claim Rejections under 35 USC §103 (Palasis)*

Claim 41 stands rejected under 35 USC §103(a) for allegedly being obvious over Palasis (Office Action at page 4). In particular, the Office Action asserts that although "Palasis et al remains silent as to the material of the balloon catheter," "it would have been obvious" to use "polyamide, polypropylene, polyether block amide or polyethylene as the balloon catheter member either inherently or as mere substitution of one functionally equivalent balloon material for another within the art of balloon catheters" (Office Action at page 4).

Applicants respectfully submit that the Office Action fails to meet the applicable standard for establishing a prima facie case of obviousness by relying on the Examiner's assertion that modification of the Palasis reference was within the skill of the art at the time of the invention. "A statement that modifications of the prior art to meet the claimed invention would have been within the ordinary skill of the art at the time the claimed invention was made because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references" (MPEP 2143.01, quoting *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993)). Furthermore, "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" (MPEP 2143.01, quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)). The assertion that Palasis can

be modified to teach or suggest the materials recited in claim 42 is not supported by any reference or basis in the Office Action beside the Examiner's conclusory statement. Therefore, this rejection fails to meet the requisite basis to establish *prima facie* obviousness under 35 USC §103. Accordingly, Applicants respectfully submit that this rejection has not been formulated in a manner sufficient to establish a *prima facie* case of obviousness. Reconsideration and withdrawal of this "rejection" is requested.

*Claim Rejections under 35 USC §103 (Palasis/Barry)*

Claims 41, 44, 46-48 and 54 are rejected under 35 USC §103(a) for allegedly being obvious over Palasis in combination with published U.S. patent application US2003/0059454 ("Barry") (Office Action at page 5). In particular, the Office Action asserts that although "Palasis et al remains silent as to any dosing levels," "it would have been obvious" to use the claimed dosage ranges, including about 5 to about 500 micrograms (claims 44 and 47) and/or 0.2 to 20 micrograms per square millimeter of the outer surface area of the expandable balloon (claims 46, 48 and 54). Applicant respectfully traverses this rejection.

As a threshold matter, the Barry reference is not itself properly considered as prior art under 35 USC §102(e). The Barry reference was filed September 24, 2001, and claims priority to provisional US patent application 60/324,095 filed on September 24, 2001 ("Barry '095 provisional filing"). The pending claims of the present application is entitled to a priority date of July 12, 2002. The Barry '095 provisional filing is different, and more limited, than the Barry reference.

Accordingly, only the portion of the Barry reference supported by the disclosure of Barry '095 provisional filing by Barry is prior art under 35 USC §102(e).

The Office Action mischaracterizes the teachings of Barry that are supported by the Barry '095 provisional filing. In particular, the following assertions in the Office Action are misrepresentative of the full disclosure of Barry '095 provisional filing: (1) the Office Action alleges that Barry teaches "delivering a lipophilic bioactive material (paclitaxel) to an interior wall of a body vessel... in the range of about 5 to about 500 micrograms (50 – 345 [micrograms])" to "compatibly prevent restenosis" (Office Action at page 5); and (2) the Office Action asserts that Barry teaches "from about 0.2 to about 20 micrograms [per $mm^2$] (.6-4 [micrograms/$mm^2$], fig. 1)" to render the claimed dose obvious "since this can be determined by experimentation" (Office Action at page 5). The selected portions of Barry recited in the Office Action ignore the full teachings of the Barry '095 provisional filing.

The Barry '095 provisional filing relates to "optimization of drug dosing and drug release kinetics... to identify... the effective therapeutic window... to obtain a desired biological response," such as reduction of restenosis after placement of a stent (page 1, lines 11-16). The Merriam Webster Dictionary defines "dosage" as "the addition of an ingredient or the application of an agent in a measured dose" and "window" as "a usually narrow interval of time or range of values for which a certain condition or an opportunity exists" (Merriam-Webster online dictionary, http://www.m-w.com). The "therapeutic window" taught by the Barry '095 provisional filing describes a measured dose of a bioactive agent in a narrow

range of values for which a condition or opportunity exists to "reduce restenosis rates when compared with uncoated stents" (page 1, lines 7-8). The Barry '095 provisional filing clearly states that "both drug dose and drug release profile are significant factors for the safety and efficacy of drug coated stents" (page 3, lines 27-29, emphasis added). In particular, the teachings of the Barry '095 provisional filing are limited to a very specific "therapeutic window" to "minimize the possibility of restenosis" (page 1, line 6) evidenced by reduced vessel relaxation, fibrin accumulation, medial thinning, loss of endothelial cells and thrombus formation in porcine arteries after implantation of a stent coated with paclitaxel in a containment polymer carrier (page 2, lines 1-5 and 12-15). The "therapeutic window" of paclitaxel is clearly and specifically described by three values: (1) the "dose" of paclitaxel expressed in micrograms per square millimeter of stent surface area, (2) the total amount of paclitaxel per stent and (3) the weight percent of paclitaxel in the polymer carrier. However, the Barry '095 provisional filing alone, or in combination with Palasis, fails to provide any guidance as to the boundaries of this "therapeutic window" for any coating that is free of a containment material, such as a polymer carrier.

This rejection therefore fails to establish a *prima facie* case of obviousness under 35 USC §103 of the claimed embodiments of the present invention under existing applicable case law. Prior to the teachings of the present application, one would not have modified the teachings of Palasis or the Barry '095 provisional filing to deliver a bioactive material to an interior wall of a body vessel

from an expandable balloon having the bioactive material on the outer surface of the balloon without a containment material present.

Where multiple references are combined in formulating an obviousness rejection under 35 USC §103, there must be "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 [82 USPQ2d 1385) (2007). Where one of the references explicitly teaches that modification of another reference in the manner asserted by the Office Action will result in therapeutically undesirable effects, the requisite reason for combining the references is not present and the obviousness rejection fails to meet the applicable legal standard for a *prima facie* case. In *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, the Federal Circuit held that "in cases involving new chemical compounds, it remains necessary to identify some reason... to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound." *Takeda Chemical Industries*, 492 F3d 1350, 83 USPQ2d 1169 (Fed. Cir. 2007). In *Takeda*, the existence of a prior art reference describing a prior art "lead compound" that "exhibited negative effects, such as toxicity, or other adverse side effects" could not properly be asserted as a "starting point" for invalidating a claim to chemically similar compounds. *Takeda Chemical Industries,* 83 USPQ2d at 1175-1176. The *Takeda* court concluded that where "the closest prior art compound... exhibited negative properties that would have directed one... away from that compound....The evidence showed

that it was not obvious to try" and the applicable legal standard for obviousness under 35 USC §103 was not met. *Takeda Chemical Industries*, 83 USPQ2d at 1176.

Similarly, this rejection does not meet the applicable legal standard for obviousness under 35 USC §103, including the *Takeda* case discussed above, for at least the following two reasons: (1) both the Barry '095 provisional filing and the Palasis reference indicate that a containment material is required either to maintain the therapeutic agent as a "saturated solution" in Palasis or to maintain the therapeutic agent dose within a "therapeutic window" in the Barry '095 provisional filing; and (2) the Barry '095 provisional filing identifies "adverse effects" when the dose of the therapeutic agent is maximized by the "saturated solution" of therapeutic agent taught by Palasis.

The Barry '095 provisional filing describes a therapeutic window only for stent coatings that include a containment layer or containment material, such as a polymer in contact with the bioactive agent. In particular, the Barry '095 provisional filing discloses only stent coatings that include paclitaxel "contained within a styrene-isobutylene based block copolymer polymer" (page 2, lines 9-11). To form the device, paclitaxel may be "applied to" a metallic stent with the polymer containment material (page 1, lines 21-22 and page 2, lines 9-11) or "the stent is a degradable polymer stent that contains the paclitaxel" (page 1, lines 23-24). These "[p]aclitaxel coated metallic stents of various doses were implanted into healthy porcine arteries to determine the effect of dosage on biological response" (page 2, lines 2-5). Notably, "different weight fractions of paclitaxel in

the polymer carrier resulted in different release kinetics" (page 3, lines 3-5), with a "direct correlation between drug weight fraction in the carrier and the release rate" (page 3, lines 6-8) and a "difference in biological response resulting from the difference in paclitaxel release rate" (page 3, lines 15-17). Nowhere does the Barry '095 provisional filing disclose the therapeutic window dosage of a stent coating without this polymer, which acts as a containment layer to regulate the rate of release of the paclitaxel. As a result, the Barry '095 provisional filing does not teach or suggest a coating having a bioactive material that is not incorporated within a containment layer.

The Barry '095 provisional filing teaches that a paclitaxel dose of 4.0 micrograms/$mm^2$ (with 345 micrograms of total paclitaxel in the coating) was outside the "therapeutic window" and resulted in significant "adverse effects" including "pronounced vessel relaxation, fibrin accumulation, medial thinning, loss of endothelial cells and possible thrombus formation" at the site of implantation within a porcine artery (page 2, lines 12-15). In contrast, paclitaxel coating doses of 2.0, 1.0 and 0.6 micrograms/$mm^2$ (175, 85 and 50 micrograms of total paclitaxel, respectively) in a containment polymer resulting in a "corresponding decrease" in these "adverse effects" with lower doses. The Barry '095 provisional filing concludes that the paclitaxel dosage is preferably limited to "up to about 2.0 micrograms/$mm^2$" or lower "based on these results" (page 2, lines 22-23). The Barry '095 provisional filing therefore teaches that portions of the claimed dosage range of 0.2 to 20 micrograms per square millimeter of surface area could lead to "adverse effects." Therefore, one skilled in the art

would not be motivated to formulate a coating without a polymer containment material over the full dosage range based on the Barry '095 provisional filing.

Finally, the Barry '095 provisional filing also teaches that a coating consisting of the bioactive material in the absence of the containment polymer would have adverse therapeutic effects. The Barry '095 provisional filing teaches that increasing the weight percentage of the bioactive agent in the coating increases the release rate, resulting in negative clinical effects. For example, the Barry '095 provisional filing teaches that increasing the release rate of the paclitaxel by increasing the weight fraction of paclitaxel in a polymer coating from 8.8% to 35% resulted in a faster release rate and "noticeable fibrin accumulation, whereas slower rates... did not result in this effect" (Barry '095 provisional filing, page 3, lines 17-20). Therefore, one skilled in the art would not be motivated to formulate a coating without a polymer containment material based on the Barry '095 provisional filing.

Combination with Palasis does not remedy these shortcomings of the Barry '095 provisional filing. The Office Action's reliance on the Barry '095 provisional filing to modify the teachings of Palasis is a misplaced basis for alleging that the claimed embodiments are obvious under 35 USC §103. Like the prior art reference discussed above in the *Takeda Chemical* case, the Barry '095 provisional filing teaches that significant "adverse effects" (Barry '095 provisional filing, page 2, line 16) accompany paclitaxel doses outside of the "therapeutic window" (i.e., doses in excess of 2.0 micrograms per square millimeter, 175 total micrograms of paclitaxel and more than 8.8% paclitaxel loading in the

containment polymer coating). In contrast, the Palasis reference, as discussed above, teaches that it is "critical" that a "saturated solution" of the therapeutic agent be contacted with the blood vessel (Palasis, col. 13, lines 34-36), requiring a containment polymer (col. 10, lines 19-35) with a maximum dose of the therapeutic agent to keep the "saturated solution" "associated with the medical device" (col. 3, lines 10-15).

The combined teachings of the Barry '095 provisional filing and Palasis would suggest that the bioactive in a coating must be contained within a containment layer or containment material. Furthermore, the teachings of Palasis and the Barry '095 provisional filing contradict with respect to the dose of the bioactive material within the coating. Palasis teaches maximizing the amount of the therapeutic agent in the coating by delivery of a "substantially saturated" solution of the bioactive is critical to delivering the therapeutic agent (Palasis, col. 7, lines 35-43). In contrast, the Barry '095 provisional filing teaches that the increasing the amount of therapeutic agent in the coating above the "therapeutic window" (e.g., above about 35% of the coating) actually causes "adverse effects." Therefore, one reading Palasis in combination with the Barry '095 provisional filing would not be able to determine whether the amount of bioactive should be restricted to the amount taught for the "therapeutic window" taught by the Barry '095 provisional filing, or a higher "saturated" dose taught by Palasis.

Therefore, for at least these reasons, the combination of Palasis and Barry '095 provisional filing fails to teach or suggest the claimed embodiments being

rejected under 35 USC §103. Reconsideration and withdrawal of this rejection is requested.

**Objection to Oath/Declaration**

The Office Action objects to the oath or declaration for allegedly failing to recite a duty to disclose all information "material to patentability" (Office Action at page 2). Applicants respectfully disagree. The Oath/Declaration actually reads in relevant part:

> I acknowledge the duty to disclose information which is material to the examination of this examination in accordance with Title 37, Code of Federal Regulations, 1.56(a) (Declaration and Power of Attorney, received December 1, 2003 by USPTO, page 1)

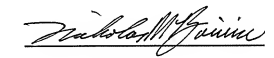
By specifically citing 37 CFR 1.56(a), this Oath/Declaration already includes a "duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section" under 37 CFR 1.56(a) (emphasis added), where "this section" refers to all of 37 CFR 1.56. Therefore, by stating that the "duty to disclose information... in accordance with Title 35, Code of Federal Regulations, 1.56(a)," the existing Oath/Declaration already recites the duty to disclose all information "material to patentability" in accordance with all of 37 CFR 1.56. Therefore, reconsideration and withdrawal of this objection is requested.

**Conclusion**

If, for any reason, the Examiner is unable to allow the application and feels that an interview would be helpful to resolve any remaining issues, he is respectfully requested to contact the undersigned attorney at (317) 636-0886.

Respectfully submitted,

Dated: January 18, 2007



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